What effects might anti-TNF α treatment be expected to have on cardiovascular morbidity and mortality in rheumatoid arthritis? A review of the role of TNF α in cardiovascular pathophysiology

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Patients with rheumatoid arthritis (RA) have an increased burden of atherosclerotic cardiovascular disease which cannot be explained by an increased prevalence of traditional cardiovascular risk factors alone. Atherosclerosis is now being viewed as an inflammatory condition and the cumulative inflammation experienced in RA may contribute to accelerated atherosclerosis. It has been hypothesised that treatment with anti-tumour necrosis factor (TNF) α in RA may reduce both intra-articular inflammation and the inflammation associated with atherosclerosis. Thus, TNF α blockade may reduce the cardiovascular morbidity and mortality associated with RA. This review examines the pathophysiological role of TNF α in atherosclerosis and the evidence to date that anti-TNF α treatment modifies this process in RA.

situation in RA is very different: chronic synovial inflammation is driving a systemic inflammatory response with levels of CRP much higher than those in the hsCRP studies. Nevertheless, the relationship between CRP and CVD holds true in inflammatory arthritis and RA. Work from the Norfolk Arthritis Register, a primary care-based inception cohort of patients with inflammatory polyarthritis, found raised baseline CRP levels to be strongly associated with death from CVD, with a hazard ratio (compared with normal CRP) of 3.9 for men and 4.2 for women.¹⁵ In a population-based incidence cohort of patients with RA from the Mayo Clinic, the erythrocyte sedimentation rate (ESR) was both a baseline and a time-dependent predictor of cardiovascular death.¹⁶ In both studies, the association between inflammatory markers and cardiovascular death persisted after adjustment for traditional cardiovascular risk factors. Although the nature of the relationship between CRP and cardiovascular events is not clear from these epidemiological studies—Is it causal? Is it a surrogate marker?—they do strongly support a role for inflammation in accelerating the progression of CVD.

Such clinical endpoint cohort studies rely upon long periods of prospective follow-up or accurate retrospective data regarding cumulative inflammatory burden. An alternative approach increasingly used in CVD studies is to measure subclinical atherosclerosis non-invasively, allowing exploration of the progression of atherosclerosis before the onset of clinically significant events. Increased carotid artery intima media thickness (IMT), an indicator of generalised atherosclerosis, has been documented in patients with RA without a prior history of CVD both with^{17 18} and without¹⁹ traditional risk factors. It is of interest that, although there was no relationship between inflammatory markers and carotid IMT (isolated inflammatory markers may not be a good marker of cumulative disease activity),^{17 19} there was an association between increased IMT and a history of extra-articular RA.¹⁹ One study explored the

There is increasingly strong evidence that patients with rheumatoid arthritis (RA) experience accelerated atherosclerosis. This results in an approximately twofold increase in mortality from myocardial infarction (MI) and stroke compared with the general population.^{1–6} The increased mortality is apparent within the first 8–10 years from symptom onset⁷ and is most marked in patients who are positive for rheumatoid factor. There is also evidence of an increased risk of non-fatal MI and heart failure.^{8–10} Although RA and atherosclerotic cardiovascular disease (CVD) share risk factors such as smoking and a poor diet, the increased risk of CVD in RA cannot be explained by traditional risk factors alone. Inflammation and treatment may each have a role. RA is now accepted as an independent risk factor for the development of CVD, with the risk being of the same order of magnitude as is seen in diabetes mellitus.¹¹ The inflammatory link is reinforced by the finding by Choi *et al*¹² that patients with RA treated with methotrexate had a 70% reduced cardiovascular mortality compared with those treated with other traditional disease modifying anti-rheumatic drugs (DMARDs) after adjusting for potential confounders.

Atherosclerosis too is now being viewed as an inflammatory condition.¹³ In healthy individuals, high-sensitivity C-reactive protein (hsCRP) has been shown to predict incident cardiovascular events in both men and women.¹⁴ However, the

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Abbreviations: CHF, chronic heart failure; CVD, cardiovascular disease; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; MI, myocardial infarction; IMT, intima media thickness; RA, rheumatoid arthritis; TNF α , tumour necrosis factor α

association between cumulative inflammation and carotid IMT, finding a positive association with cumulative ESR but not CRP.¹⁸ Another component of atherosclerosis, in addition to arterial wall thickening, is arterial stiffness. This is increased in patients with RA compared with normal controls.^{20–21} Again, the link with inflammation is present with a correlation between arterial stiffness and both disease duration and inflammatory markers (CRP, interleukin (IL)6).²⁰

These findings suggest that reducing the burden of inflammation in RA—particularly sustained reduction of the ESR and/or CRP—might be expected to slow the progression of atherosclerosis and so improve the cardiovascular outcome of these patients.

ANTI-TNF TREATMENTS FOR RA

The cytokine tumour necrosis factor α (TNF α) plays a key role in the pathogenesis of RA.²² The introduction of the anti-TNF α treatments infliximab, etanercept and adalimumab has dramatically improved the outcome of severe RA.^{23–25} A question of major interest within the rheumatology community is whether anti-TNF α treatment will, by reducing inflammation and improving the joint symptoms of RA, also reduce the burden of CVD. In order to understand what effects anti-TNF α treatment might have on CVD, we need to understand how TNF α fits into the pathophysiology of atherosclerosis and CVD. The purpose of this review is to examine the role of TNF α in CVD, as well as reviewing the current evidence that anti-TNF α treatment has an effect upon cardiovascular risk factors and outcomes.

ROLE OF TNF α IN THE PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE

Classical risk factors

Cytokines are important in directing transient alterations in lipid levels and insulin resistance at times of acute inflammation. However, in a setting of chronic inflammation, states of insulin resistance and altered lipid metabolism can be induced. TNF α plays a major part in impeding insulin-mediated glucose uptake in skeletal muscle and increasing circulating free fatty acids.²⁶ Increased levels of CRP have recently been associated with increased insulin resistance in patients with RA, although this was not independent of waist circumference²⁷ (abdominal obesity is a major determinant of insulin resistance in the general population and abdominal fat derived adipokines may contribute to the raised CRP). Dyslipidaemia may be associated with the inflammatory response of RA, with raised levels of low-density lipoprotein (LDL) being found in patients with RA compared with controls.²⁸ The link between lipid profile and inflammation in RA is suggested by observed changes following treatment. After treatment with prednisolone (and non-steroidal anti-inflammatory drugs), changes in high-density lipoprotein (HDL) and total cholesterol were seen to correlate with changes in ESR.²⁹ In the COBRA study, high-dose steroids used in conjunction with other DMARDs were shown to improve the atherogenic index (ratio of total cholesterol to HDL) with a linear association between the disease activity score (DAS28³⁰) and the atherogenic index.³¹

Atherosclerosis

The pathway leading to cardiovascular events begins with the initiation of atherosclerosis, moving through plaque development to possible plaque rupture and thrombus formation, potentially resulting in clinically detectable endpoints. Inflammation is implicated at all stages of atherosclerosis.

Endothelial cell activation has been hypothesised to link RA with an early initiation of atherosclerosis,³² with persistent endothelial activation being termed endothelial cell dysfunction. TNF α may mediate endothelial dysfunction both directly

and indirectly.²⁶ Adhesion molecules are upregulated in response to pro-inflammatory cytokines including IL1 β and TNF α , leading to the migration of monocytes into the vessel wall intima. Monocytes are then transformed into macrophages which scavenge oxidised LDL, thus becoming foam cells and forming the fatty streak. These foam cells express pro-inflammatory cytokines including TNF α which promote further adhesion molecule expression and architectural progression of the atherosclerotic plaque.³³ One study of patients with RA failed to find a correlation between the level of TNF α and adhesion molecules in the blood, but did find a relationship with IL6.³⁴

Plaque rupture leads to around three-quarters of acute MIs, although many episodes of plaque rupture are asymptomatic. Fissure of the fibrous cap that separates the thrombogenic lipid-rich core of the plaque from the circulation also involves inflammation. Little is known of this mechanism. Pro-inflammatory cytokines including interferon γ and TNF α are synthesised in the plaque.³⁵ They are thought to increase collagen breakdown in the fibrous cap, acting via matrix metalloproteinases. They also inhibit collagen repair by local vascular smooth muscle cells¹³ and promote vascular smooth muscle cell apoptosis.³⁶

Haemostasis

TNF α renders local endothelium prothrombotic and promotes the expression of tissue factor on monocytes.³⁷ In addition, TNF α has a systemic role in upregulating proteins involved in haemostasis, leading to a prothrombotic state. Around one-third of acute coronary syndromes result from superficial erosion of a markedly stenotic and fibrotic plaque without plaque rupture,³⁸ and thus thrombus formation may depend upon a systemic hypercoagulable state. Patients with RA have raised levels of fibrinogen, von Willebrand factor and tissue plasminogen activator antigen compared with the general population.³⁹ In a Swedish cohort of patients with RA, prothrombotic markers predicted cardiovascular events.⁴⁰ Specific to the cerebral circulation, TNF α has been implicated in “priming” the vasculature to be sensitive to brain ischaemia, known as the Schwartzman reaction.⁴¹

Post-event repair

TNF α has important roles in both the lead up to cardiovascular events and in their subsequent recovery. In the post-MI setting, as in many other situations, TNF α has pleiotropic effects dependent upon its concentration and can influence outcome in both directions. TNF α has a protective role in the physiological adaptive response to injury and limits infarct size⁴² although, when overexpressed, it can lead to maladaptive effects such as promoting left ventricular dysfunction.⁴³ Following a stroke, TNF α interacts with other mediators to influence repair and tolerance.⁴⁴

Patients with severe chronic heart failure (CHF) have higher circulating levels of TNF α than healthy subjects.⁴⁵ Raised levels of TNF α are also a marker of poor prognosis,⁴⁶ suggesting a possible therapeutic use for anti-TNF α treatment. However, initial trials were disappointing (see below).

Given this body of evidence linking inflammation (and specifically TNF α) to the initiation and progression of CVD, one might expect anti-TNF α treatment to reduce the burden of CVD in patients with RA. Hypothetically, this might act at many levels. It may potentially improve lipid profiles, reduce insulin resistance, prevent fatty streak formation, stabilise plaques, reduce thrombus formation and/or improve recovery (fig 1). However, the complexities of cytokine pathways and interactions often mean that what initially seems biologically plausible may not ultimately occur. The following section will review the evidence to date that anti-TNF α treatment modifies CVD.

Figure 1 Relationship between tumour necrosis factor α (TNF α) and cardiovascular disease. TNF α promotes dyslipidaemia and insulin resistance, both of which are traditional risk factors for atherosclerosis. TNF α upregulates adhesion molecules, leading to fatty streak formation and the initiation of atherosclerosis, and is involved in the inflammation leading to plaque rupture. TNF α may promote thrombophilia, encouraging thrombotic events. Post-ischaemic event repair may be modified by inflammatory cytokines. Anti-TNF α treatment may exert an influence at any of these stages.

CURRENT EVIDENCE THAT ANTI-TNF α TREATMENT MODIFIES THE CVD BURDEN IN RA

Classical risk factors

Several studies have explored the effect of anti-TNF α treatment on the lipid profile in patients with RA. Most show an increase in HDL cholesterol,^{47–50} although there is disagreement regarding how long this effect is sustained. After 6 weeks of treatment with infliximab, total cholesterol and HDL cholesterol both increased significantly from baseline but with no change in the atherogenic index,^{47–48} a pattern that persisted with treatment to 30 weeks.⁴⁸ Popa *et al*⁴⁹ found a similar increase in total and HDL cholesterol following 2 weeks of treatment with adalimumab, but with no change in LDL cholesterol or triglyceride measurements and a beneficial reduction in LDL:HDL ratio. The same group have recently found that these changes are not sustained, returning to baseline by 6 months of follow-up.⁵¹ Another study found a contrasting reduction in HDL cholesterol the day after treatment with infliximab, but with no change in HDL cholesterol across 6 weeks of treatment.⁵² No conclusions can be drawn from these inconsistent short-term findings regarding potential longer term clinical implications. It also remains possible that changes observed following anti-TNF α treatment are not directly attributable to that treatment, but instead reflect changes in co-therapy such as steroids and statins.

Danish investigators have explored the effect of etanercept on insulin resistance in obese patients with type 2 diabetes. They found that, while inflammatory markers fell in the group treated with etanercept, there were no changes in fasting levels of glucose, insulin or lipids after 1 month of treatment.⁵³ However, this patient group did not have RA or chronic inflammation. In contrast, a study undertaken in patients with RA or ankylosing spondylitis found that infliximab infusions had a beneficial effect on insulin sensitivity in the tertile of patients with the worst insulin resistance.⁵⁴ It was not clear whether this improved insulin sensitivity correlated with an improvement in systemic inflammation. In a Spanish study of 27 patients with RA there was a significant reduction in insulin levels, lowering of the insulin/glucose index and improvements in insulin resistance 2 h after infliximab infusion.⁵⁵ The authors did not investigate whether this effect was sustained in the longer term.

Atherosclerosis

It has been hypothesised that TNF α inhibition may improve endothelial function in patients with RA. There is evidence to support this, although the duration of the effect is not clear. One study found an improvement in endothelium-dependent

vasodilation at 12 weeks after a course of infliximab treatment at weeks 0, 2 and 6, with no change in endothelium-independent vasodilation.⁵⁶ Another study found improvements in flow-mediated dilation following infliximab, although these changes were transient and had returned to baseline by the time of the next infusion.⁵² A Spanish group explored the temporal relationship in patients established on infliximab. They found the improvements in endothelial function to be sustained at days 2 and 7 after the infusion, but the majority of patients had lost the effect by 28 days after the infusion.⁵⁷ Two studies have examined the change in arterial stiffness—a marker of vascular dysfunction that is influenced by both endothelial cell function and vascular smooth muscle tone—in response to anti-TNF α drugs in patients with RA. Both found no change in the augmentation index (a composite measure of systemic arterial stiffness and wave-reflection amplitude or intensity) despite reductions in markers of inflammation and disease activity scores.^{58–59} However, the larger study did find a significant reduction in aortic pulse-wave velocity following anti-TNF α treatment.⁵⁹

Hypothesising that anti-TNF treatment might slow progression of subclinical atherosclerosis, the same Spanish group measured carotid IMT in eight patients with RA before and after a median of 3 years of anti-TNF α treatment and compared progression with matched controls.⁶⁰ There was no significant difference between the two groups. Despite this negative finding, it remains plausible that TNF α inhibition may affect initiation or progression of atherosclerosis. However, such treatment can only act at time points where TNF α has pathophysiological importance. Thus, in order to measure such effects, investigators must study the appropriate patient population to match their hypothesis; for example, patients without evidence of any atherosclerosis (to study initiation of atherosclerosis) or with unstable plaques (to study plaque stabilisation).

As already mentioned, TNF α has been implicated in sensitising the cerebral circulation to ischaemic damage. In an animal model of this paradigm, strokes were completely prevented by administration of a recombinant TNF α receptor.⁴¹ Further work in preclinical stroke models has suggested a potential benefit of TNF α converting enzyme inhibition.⁶¹

Clinical endpoints

Raised levels of TNF α in CHF alongside the powerful predictive value of high levels of TNF α on adverse outcome in CHF led to studies of anti-TNF α treatment in severe CHF. Two studies of etanercept were terminated early when interim analysis found

a lack of efficacy,⁶² and high-dose infliximab was shown to be detrimental in patients with moderate to severe CHF.⁶³ As a consequence, severe heart failure is a contraindication to anti-TNF α treatment in patients with RA.⁶⁴ These original trials were not undertaken in a population with chronic inflammation where the balance of TNF α is very different. Kwon *et al*⁶⁵ studied 47 cases (38 with RA) reported to the US Food and Drug Administration's MedWatch program of heart failure after anti-TNF α treatment.⁶⁵ Half of the patients with new onset heart failure (19/38) had no risk factors and 10 patients were under 50 years of age. These findings, despite the limitations of spontaneous pharmacovigilance, raise concerns. More recent work, however, has suggested that there may be a protective effect of anti-TNF α treatment on self-reported diagnosed or treated heart failure in patients with RA.¹⁰ However, when limiting the analysis to patients without a past history of CVD (and thus avoiding selection bias), there was no observed protective effect of anti-TNF α treatment.

Clinical trials of anti-TNF α treatments in RA have not focused on cardiovascular events and, indeed, are not sufficiently powered to detect modest changes in the incidence of rare events such as MIs. We must therefore rely on large observational studies to examine clinical endpoints. In patients from the Southern Swedish Arthritis Treatment Group, the risk of a first cardiovascular event was around half that of anti-TNF α naïve patients with RA.⁶⁶ However, these results are based on small numbers of events ($n = 13$) in the anti-TNF α treated cohort. Unfortunately, because of the small numbers of events, the authors were not able to explore individual events and combined all cardiovascular events together, including events that do not share a common pathophysiological pathway. Furthermore, the authors were not able to adjust for several possible confounders such as smoking and disease activity. In nested case-control studies using large US healthcare utilisation and insurance claims databases, rates of MI in patients with RA treated with biological therapy were not significantly different from rates in patients treated with methotrexate monotherapy (odds ratio 1.8 (95% confidence interval (CI) 0.5 to 6.8))⁶⁷ or no DMARDs (1.30 (95% CI 0.92 to 1.83)).⁶⁸ However, again the authors were not able to adjust for several important confounders including disease severity. The rate of stroke was also found not to be significantly increased or decreased in biologically treated patients compared with those treated with methotrexate.⁶⁷ Because anti-TNF α treatment is only used in patients with the most severe RA, there may be confounding by indication; one might expect these patients already to have an increased risk of CVD, given their greater burden of inflammation. The above findings, in the absence of adjustment for disease severity, must be interpreted with care.

CONCLUSION

There is a strong body of evidence to support a theoretical role for anti-TNF α treatment in reducing the cardiovascular burden associated with RA. Research into this area needs to be targeted towards pathways and endpoints to which TNF α is integral. Grouping all cardiovascular events together may be uninformative. Furthermore, specific events may need to be further subdivided: for example, anti-TNF α treatment may have an effect on ischaemic strokes but not on intracerebral bleeds. As follow-up time accrues for patients followed by the national registries, we are likely to understand better the effect of anti-TNF treatment on both cardiovascular morbidity and mortality.

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